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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,344	06/09/2005	Guy Vergnault	28069-608 NATL	3745
<div>35437 7590 02/21/2008 MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO 666 THIRD AVENUE NEW YORK, NY 10017</div>				
			EXAMINER EBERHARD, JEFFREY S	
			ART UNIT 1615	PAPER NUMBER
			MAIL DATE 02/21/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/538,344

Applicant(s)

VERGNAULT ET AL.

Examiner

Jeffrey S. Eberhard, Ph.D.

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12, 14-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 June 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/13/2006.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Drawings

Figures 1 and 2 are objected to under 37 CFR 1.83(a) because they fail to show a level of detail allowing differentiation of physical features as described in the specification (page 13, lines 18-27). Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 8 and 14-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano (US 5,506,222) in view of Schäfer-Korting *et al.*, ("Delivery of Lipophilic Compounds with Lipid Nanoparticles – Applications in Dermatics and for Transdermal Therapy," in *Lipospheres in Drug Targets and Delivery*, CRC Press (2005), Claudio Nastruzzi, Editor), in further view DrugBank (<http://redpoll.pharmacy.ualberta.ca/drugbank>) and of references cited in Schäfer-Korting (Reference 9, Mehnert and Mäder, "Solid lipid nanoparticles: Production, characterization and applications," *Adv. Drug Deliv. Rev.* (2001) 47:165-196; and Reference 29,

zur Mühlen, *et al.*, "Solid Lipid Nanoparticles for Controlled Drug Delivery," *Eur. J. Pharm. Biopharm.* (1998) 45:149-155).

Regarding claims 1 and 2, the instant Application is drawn to a formulation comprising spironolactone in an oriented crystalline lipid matrix for application to skin or mucosa. Stefano teaches spironolactone for topical application (column 11, claim 1) in a lipid matrix (column 12, claim 2, substituted unsaturated fatty acids), but is silent regarding oriented crystalline nanoparticles. Schäfer-Korting teaches solid lipid nanoparticles (50 to 1000 nm) for topical application (Section 7.2 and Reference 9) having a drug enriched core with a lipid crystal shell, formed as a function of the lipid's melting point and the relative solubilities of the drug and the lipid (page 133, Section 7.6, Figure 7.3, and Reference 29). The drug enriched core is formed when the drug precipitates before the lipid crystallizes. Because spironolactone (7 α -acetylthio-3-oxo-17 α -pregn-4-ene-21,17-carbolactone) is practically insoluble in water and has a Log P of 4.3 (*See* Drugbank entry for Spironolactone), the lipid nanoparticulate form of the drug forms such that the lipid crystal shell's hydrophilic "side" would face "outward," because the hydrophobic "side" would face "inward" toward the encapsulated lipophilic spironolactone. Schäfer-Korting citing Mehnert and Mäder (at Section 1.2) further teaches that photon correlation spectroscopy is the state of the art measurement technique for particle size determinations of particles in the range of "a few nanometers to 3 μ m."

Because enhanced skin permeation (Schäfer-Korting, section 7.10.2) occasioned by use of the nanoparticulate dosage form, obviates the need for additional formulation components (*e.g.*, Stefano's permeation enhancers) it would have been obvious to the person of ordinary skill in the art at the time the invention was made to have combined the formulation taught by Stefano

with the liquid crystalline nanoparticulate lipid taught by Schäfer-Korting to obtain a topical dosage form of spironolactone with bioavailability resulting from the use of nanoparticulates rather than formulated permeation enhancers.

Regarding claims 8, 14-19, 23 and 24, Schäfer-Korting and Stefano are discussed above, with Stefano teaching the use of topical spironolactone compositions to treat the effects of increased androgenic activity including acne and hirsutism (Abstract). These topical formulations comprise glyceryl monoesters, *e.g.* glyceryl monostearate (column 6, line 26), which are inherently crystalline under certain conditions of temperature, and other components of a cosmetically suitable cream base (column 4, lines 54 to 63) with additional excipients designed to promote drug delivery at the active site within the skin strata in order to obtain a therapeutic effect (column 5, Example 1 *et seq.*). Thus, it would have been obvious to the artisan of ordinary skill to combine the topical spironolactone formulation and dosing information of Stefano with the skin permeation enhancing nanocrystallinity of Schäfer-Korting to treat the effects of increased androgenic activity (*e.g.*, acne and hirsutism) in patients with a need for such treatment using a topical preparation.

Regarding claim 20, combining the skin permeation enhancing oriented crystalline network system of Schäfer-Korting with the “incorporated substance for use in topical treatment of acne” (*e.g.*, spironolactone) as taught by Stefano would have been obvious to a person of ordinary skill in the art to obtain a topical dosage form with a bioavailable active ingredient resulting from the use of nanoparticulates rather than additional formulation components.

Regarding claims 21 and 22, Schäfer-Korting, Schäfer-Korting citing Mehnert and Mäder, and Stefano are discussed above, but they do not teach specific particles in the size range

of from 300 to 900 nanometers. Schäfer-Korting teaches (Section 7.10.2.) that drug penetration into the skin strata is strongly related to particle size with “particles smaller than 400 nm [proving] to be most potent.” The adjustment of particular conventional working conditions (*e.g.*, determining result effective particle sizes beneficially taught by the cited references, especially within the broad ranges recited in claims), as well as affecting desired skin penetration (bioavailability of the active ingredient), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the artisan of ordinary skill. Accordingly, this type of modification would have been well within the purview of the person of ordinary skill in the art and no more than an effort to optimize results.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Schäfer-Korting in further view of Lane (<http://ches.ua.edu/departments/nhm/faculty/lane/nhm454/McWCh11&12fats.pdf>).

Stefano and Schäfer-Korting are discussed above with Stefano further teaching glycerol monoesters (*e.g.*, glyceryl monostearate, column 6, line 26), but they are silent regarding lipid crystallization temperature. Lane teaches lipids with a crystallization temperature in the recited range (70°C, page 1, lower right), and further teaches β -crystal of the monoglycerides of C₁₈ fatty acids (pages 2-3). Adjustment of crystallization temperature by judicious selection of formulation components such as these glyceryl monoesters yields an extent of crystallinity useful in topical formulations for transporting spironolactone through the skin strata, and would have been well within the purview of a person of ordinary skill in the art at the time the invention was made.

Claims 6, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Schäfer-Korting in further view of Hansen (US 6,228,383 B1) and Kirk-Othmer (Kirk-Othmer Encyclopedia of Chemical Technology (2001), Wiley Interscience.

Regarding claims 6 and 7, Stefano and Schäfer-Korting are discussed above, but are silent regarding the solvent in which the nanoparticulate is formed. Hansen teaches that the lipid crystals are formed from polar liquids such as water and glycerol (column 6, lines 23 to 53), and that the lipid crystals are comprised of glyceryl monoesters of C₁₈ fatty acids (Id.). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the nanoparticulates taught by Stefano and Schäfer-Korting with the solvent and lipid formulation components (specifically their inherent physical properties) taught by Hansen in order to obtain a product with the physical properties necessary to effect a solid state product at a temperature range suitable for typical topical cosmetic preparations.

Regarding claims 9-12, Hansen and Schäfer-Korting are discussed above with Hansen further teaching that the composition may be characterized as a suspension (column 14, line 46, thus in view of Schäfer-Korting a “nanosuspension”) and that it further comprises a stabilizer (*e.g.*, emulsifying agent, antioxidant, preservative, solubilizing agent, column 14, lines 52-67), which would have been an obvious addition to the formulation in order to maintain the suspension over the time and temperature ranges required to yield a useful product.

Hansen and Schäfer-Korting are both silent regarding sodium docusate as a stabilizer *per se*, but the person of ordinary skill in the art would recognize the term “stabilizer” as referring to any of a number of classes of compounds including surface active agents. Hansen teaches

“solubilizing agents” (column 14, line 65), and as indicated in Kirk-Othmer, sodium docusate is a surface active agent (*i.e.*, solubilizing agent) used in pharmaceuticals (“Gastrointestinal agents, page 16, second full paragraph). Thus, the claimed stabilizer is equivalent to the teachings of Hansen in view of Kirk-Othmer.


Application Status and Examiner Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey S. Eberhard, Ph.D. whose telephone number is (571) 270-3289. The examiner can normally be reached from 6:30 am to 3:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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